REMARKS

Claims 1-13 are pending in the application. Claims 3, 4, and 12 have been cancelled by this amendment. New claims 19 and 20 have been added Therefore, claims 1, 2, 5-10, 13, 19, and 20 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. The amendment is necessary to eliminate rejections under 35 U.S.C. §103. This amendment was not presented earlier because applicants believed, and still believe, that the amendments filed December 9, 2001 overcame the outstanding rejections. The amendment should be entered because it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

The courteous interview granted by the examiners to applicants' undersigned attorney on November 14, 2002 is hereby noted with appreciation. At the interview, the claimed invention and the form of the article of manufacture claims were discussed.

THE CLAIMED INVENTION

The present invention provides an article of manufacture for human pharmaceutical use comprising a package insert with chronic dosage information, a container, and an oral dosage form comprising a PDE5 inhibitor having an IC_{50} less than 10 nM and effective in unit dosages of about 1 mg to about 10 mg/dosage form. The package insert provides language consistent with a chronic dosing regimen characterized by administration of the PDE5 inhibitor for at least three consecutive days to treat sexual dysfunction and improve vascular conditioning, and that the maximum dosage of the PDE5 inhibitor is about 10 mg per day.

The beneficial effects of a chronic dosing regimen were observed in clinical studies and through the discovery that the chronic administration of a claimed PDE5 inhibitor improves or conditions the vasculature such that the corpus cavernosum smooth muscle tissue responds to therapy at PDE5 inhibitor doses *below* that required to yield the same response with on-demand or acute therapy.

On-demand therapy using a PDE5 inhibitor to treat erectile dysfunction is the *only* currently available therapy employing a PDE5 inhibitor. In on-demand therapy, a sufficiently high dose of a PDE5 inhibitor is administered orally prior to anticipated sexual activity. The individual then must wait a sufficient time for the PDE5 inhibitor to perform its function before engaging in sexual activity. Finally, sexual activity must be performed within a short finite time period, i.e., within a relatively few hours, because the beneficial effects of the PDE5 inhibitor subside.

On-demand therapy presently is practiced in the treatment of erectile dysfunction using VIAGRA® (i.e., sildenafil), which is taken orally in relatively large doses (e.g., at least 25 mg up to 100 mg) about an hour prior to sexual activity. In addition, the present VIAGRA on-demand therapy can be adversely affected if the individual has a meal in the time period shortly before PDE5 inhibitor dosing.

The present claims are based on detailed experiments and clinical trials, and the unexpected observations that sexual dysfunction can be treated using a chronic, low dose of a PDE5 inhibitor having an IC_{50} value for inhibition of PDE5 less than 10 nM *and* a sufficient bioavailability to be effective in about 1 mg to about 10 mg unit oral dosages (e.g., claim 1). Claims 5, 10, and 13 recite additional features and especially preferred PDE5 inhibitors useful in a present article of manufacture. In particular, note the unexpected results set forth in Examples 6 and 7 of the specification.

A chronic dosing regimen of about 1 to about 10 mg of a PDE5 inhibitor for at least three consecutive days also provides other benefits including (a) spontaneity in sexual relations, (b) a return to normalcy, i.e., the patient is not required to plan sexual activity around administration of the PDE5 inhibitor, (c) unexpected efficacy for such a low oral dose of PDE5 inhibitor, including an observation of a greater response to the PDE5 inhibitor from a lower chronic PDE5 inhibitor dose than to the currently labeled 25 mg acute, on-demand dose of sildenafil, (d) lower toxicity attributed to a lower dose of PDE5 in-

hibitor, and (e) no to low adverse effects attributed to the selective PDE5 inhibitor and a low dose.

Overall, it has been demonstrated that chronic dosing of a PDE5 inhibitor having the properties enumerated above, and administered for at least three consecutive days (with no upper limit), provides the same or improved efficacy at about 1 mg to 10 mg than a higher on-demand dosage (i.e., at least 25 mg) that presently is administered. The enhanced efficacy demonstrated by low daily dosing of a PDE5 inhibitor in treating erectile dysfunction is not dependent on drug accumulation, but rather results from improved vascular responsiveness when the PDE5 inhibitor is present continuously, or essentially continuously, in plasma.

The "vascular conditioning" effect has not been demonstrated previously with PDE5 inhibitors in particular, or PDE inhibitors in general. In particular, vascular conditioning has not been observed in on-demand dosing of a PDE5 inhibitor, or in individuals taking an acute PDE5 inhibitor dose for a short time span. It is believed that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, for example, after about three consecutive daily doses of up to 10 mg, preferably after five consecutive days of daily dosing, and more preferably after seven consecutive days of daily dosing. In addition, after about three days of consecutive daily dosing, intermittently missing one chronic dose may lead to a reduction in vascular conditioning, but not a complete loss of conditioning, and thus would not be expected to substantially reduce the benefits associated with chronic dosing.

It has been theorized that vascular conditioning is caused by a partial or complete reversal of circulatory dysfunctions in penile circulation arising from conditions such as diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors. These conditions result in thickening of the arterial wall, decreased arterial compliance, and decreased responsiveness to endogenous vasodilators, such as nitric oxide.

The presently claimed invention provides unexpected advantages over the currently available VIAGRA® pharmaceutical product that utilizes sildenafil as the PDE5 inhibitor. While sildenafil has obtained significant commercial success, problems in the treatment of erectile dysfunction (ED) still exist. First, ED therapy using sildenafil is based on an on-demand therapy. "On demand" dosing is an acute administration of a drug for treating erectile dysfunction prior to expected sexual activity. The user, therefore, must plan ahead, and, as presently labeled, ingest a relatively large oral dose (i.e., at least 25 mg) of sildenafil at least one hour prior to engaging in sexual activity. The onset of beneficial effects also may be delayed when sildenafil is administered with a meal.

Second, the relatively large on-demand dose of sildenafil results in significant adverse side effects, including facial flushing (10% incidence rate). Thus, even with the commercial availability of sildenafil, there remains a need for improved pharmaceutical products that are useful and more convenient in treating sexual dysfunction. The present

claims are directed to an article of manufacture that meets this unrealized need.

THE FORM OF THE CLAIMS

The present claims are in the form of an "article of manufacture." During the interview, it was agreed that the present claims are "proper," i.e., within the statutory classes of invention of 35 U.S.C. §101. The examiners contended, however, that the claims should be presented as method claims, for example, originally filed and now-cancelled claims 14-18. Claims 14-18 will be pursued in a divisional application.

In particular, the examiner states at page 7 of the Office Action, second full paragraph:

> "Applicant also argues that a chronic dosing regimen for at least three days is not taught by the prior art. Note that the instant claims are not method claims, they are claims drawn to a product/article of manufacture. The recitation of a dosage regimen in a package insert attached to an article of manufacture does not further limit a claim drawn to an article of manufacture."

It is submitted that this reasoning is incorrect in view of the case law discussed below. In particular, the present claim is *not* directed solely to the insert and the indicia thereon. The claims recite elements (a)-(c), including an oral dosage form of a PDE5 inhibitor having specifically claimed features, a container for the oral dosage form, and an insert accompanying the container providing instructions on

the *chronic* use of the oral dosage form. As discussed in the following case law, *all* elements of a claimed combination must be considered when a claim is examined for patentability, and the insert cannot be considered independently.

In *Application of Paul J. Miller*, 418 F.2d 1392 (1969), the CCPA stated:

> "It is noted, first, that the examiner recognizes the invention of the appealed claims for what it is, namely, a combination of three elements constituting a 'manufacture' 35 U.S.C. § 101. There is no assertion that the *claimed* invention is non-statutory subject matter." (418 F.2d at 1395, emphasis in original).

That is precisely the situation in this application. Further, the examiners acknowledged that the present "article of manufacture" claims are proper and within the patentable subject matter of 35 U.S.C. §101.

The court in *Miller* went on to state at page 1396:

> "As for the examiner's characterization of the indicia and legend as 'unpatentable printed matter,' we note that the examiner himself recognizes the fact that printed matter, in an article of manufacture claim, *can* be given 'patentable weight.' He did so in allowing claims. His characterization of printed matter as 'unpatentable' is beside the point; no attempt is here being made to patent printed matter as such. The fact that printed matter *by itself* is not patentable subject matter, because nonstatutory, is no reason for ignoring it when the claim is directed to a combination. Here there is a new and unobvious functional relationship between a measuring *receptacle*, volumetric *indicia* thereon indicating volume in a

certain ratio to actual volume, and a *legend* indicating the ratio, and in our judgment the appealed claims properly define this relationship. . . .

The solicitor seeks some support for sustaining the rejection in In re Sterling, 70 F.2d 910, 21 CCPA 1134, but we find none therein. . . . The solicitor seems to urge that we *ignore* the claim limitations to the indicia and legends because they are printed and because printed matter is not patentable subject matter by itself. For reasons indicated above, we reject that argument." (Emphasis in original.)

In *In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983), the court stated:

"Differences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter.[8] Under section 103, the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. The claim must be read as a whole. If the board means to disregard that basic principle of claim interpretation, we must reverse the rejection as a matter of law.

If, instead, the board sought only to construe and apply *Miller* within the context of the section 103 rejection, we find no error in the board's articulation of the law. Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability. Although the printed matter must be considered, in that situation it may not be entitled to patentable weight. This, apparently, was the board's conclusion with respect to Gulack's invention.

However, because we find that the digits of Gulack's invention are functionally related to the band, and because Wittcoff fails to disclose or suggest the subject matter recited in the appealed claims, considered as a whole, we reverse.

[8] A 'printed matter rejection' under § 103 stands on questionable legal and logical footing. Standing alone, the description of an element of the invention as printed matter tells nothing about the differences between the invention and the prior art or about whether that invention was suggested by the prior art. A printed matter rejection is based on case law antedating the 1952 patent act, employing a point of novelty approach. The 1952 act legislatively revised that approach through its requirement that the claim be viewed as a whole in determining obviousness. The CCPA has considered *all* of the limitations of the claims, including the printed matter limitations, in determining whether the invention would have been obvious. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (Cust. & Pat. App. 1974); *In re Cavrich*, 451 F.2d 1091, 172 USPQ 121 (Cust. & Pat. App. 1971). In *Royka*, 490 F.2d at 985, 180 USPQ at 583, the CCPA, notably weary of reiterating this point, clearly stated that printed matter may well constitute structural limitations upon which patentability can be predicated."

The *Gulack* court went on to state:

"Similarly, in examining Gulack's invention, we find that a functional relationship does exist between the printed matter and the substrate. A functional relationship of the precise type found by the CCPA in *Miller*--to size or to type of substrate, or conveying information about substrate--is not required. What is required is the existence of *differences* between the appealed claims and the prior art sufficient to establish patentability. The bare presence or

> absence of a specific functional relationship, without further analysis, is not dispositive of obviousness. Rather, the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate. With these thoughts in mind we turn now to examine the obviousness of the appealed claims in light of the cited references, Wittcoff." (703 F.2d at 1386.)

In the present claims, a functional relationship exists between the package insert and the oral dosage form, and the claims define this relationship. In particular, the functional relationship is between an oral dosage form containing a *low* dosage of a specifically claimed PDE5 inhibitor and an insert providing that the oral dosage form can be administered chronically (for at least three consecutive days and at a low claimed dose) to treat ED and to improve vascular conditioning. Without the insert, the user of the claimed article of manufacture would not be informed of the new and unobvious ability to take a chronic low dose of a claimed PDE5 inhibitor (as opposed to the currently practiced on-demand therapy), and effectively treat ED while avoiding disadvantages associated with on-demand PDE inhibitor therapy for ED. As discussed hereafter, the cited art is silent with respect to chronic dosing of a PDE5 inhibitor to treat ED.

Applicants further contend that if a claim is allowable when written as a method (as suggested by the examiners), then an article of manufacture claim reciting the same features as the method claim also is allowable.

THE AMENDMENTS TO THE CLAIMS

Dependent claims 5-9 have been amended to conform in scope to independent claim 1. Claim 10 has been amended to more specifically recite preferred PDE5 inhibitors.

New independent claims 19 and 20 are supported by originally filed independent claim 1 and dependent claim 7.

As discussed at the interview, no upper limit for the number of consecutive days of chronic dosing exists. An individual can ingest the oral dosage form, chronically, for as long as desired. Treatment resides in having an effective amount of a PDE5 inhibitor continuously, or essentially continuously, in plasma (specification, page 12, lines 21-27). Also see specification, page 7, lines 10-29.

THE REJECTIONS

Double Patenting

Claims 1-13 stand rejected under the judicially created doctrine of obviousness-type double patenting over various claims of copending U.S. Patent Application No. 09/558,911, now U.S. Patent No. 6,451,807. Applicants have filed a terminal disclaimer concurrently with this amendment to overcome this obviousness-type double patenting rejection.

However, it should be noted that the basis of the double-patenting rejection is incorrect, and that the terminal disclaimer has been filed merely to facilitate prosecution. The invention claimed in U.S.S.N. 09/558,911 is directed to a treatment of ED using a

PDE5 inhibitor possessing specific potency and selectivity properties. These properties avoid or reduce adverse side effects associated with PDE5 inhibitor-mediated ED treatment. U.S.S.N. 09/558,911 is *not* directed to a chronic low dosing of a PDE5 inhibitor to treat ED.

Further, as discussed above, it is not only the presence of an insert in an article of manufacture, but the functional relationship between the insert and the oral dosage form of the article that should be considered. The present insert functions in facilitating use of the enclosed oral dosage form for a chronic treatment of ED. The insert is not directed to precautions. In U.S.S.N. 09/558,911, the insert functions in facilitating use of a PDE5 inhibitor to treat ED in individuals who could not or would not undergo treatment because of adverse side effects or because they are at a higher risk when using present-day PDE5 on-demand therapy for ED.

Rejections Under 35 U.S.C. §103

Claims 1-9 stand rejected under 35 U.S.C. §103 as being obvious over WO 96/32003 (WO'003) in view of WO 99/24433 (WO'433). The examiner contends that it would have been obvious to utilize a compound of WO'003 or WO'433 in a container with a package insert, and that a package insert is mandated therefor. In view of the amendments to the claims, the above comments with respect to printed matter, and for the following reasons, it is submitted that this rejection is in error and should be withdrawn.

WO'003 discloses a PDE5 inhibitor capable of treating numerous diseases and conditions, including erectile dysfunction. The examiner relies upon WO'003 for a teaching of a PDE5 inhibitor having an IC_{50} value less than 10 nM, oral administration, and a dosage of 0.5-800 mg, in tablets, for administration "once or several times per day." However, WO'003 fails to teach or suggest several of the claimed features.

For example, an IC_{50} value of less than 10 nM *alone* is not sufficient to render a compound suitable for use in the present invention. The PDE5 inhibitor also must have a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages, and at a maximum daily dose of about 10 mg. Neither cited reference, nor any other reference of which applicants are aware, teaches or suggests this combination of features.

In addition, no cited reference teaches a PDE5 inhibitor for chronic administration having the properties recited in dependent claim 5, which together with the features of claims 1 and 2, recite especially preferred compounds for use in the present invention. WO'003 absolutely fails to teach or suggest a PDE5 inhibitor having the potency and selectivity recited in these claims.

Furthermore, WO'003 merely teaches a *daily* dosage that can be administered either once per day or in multiple doses over the course of a day, i.e., "once or several times *per* day." WO'003 is totally silent with respect to a chronic administration, e.g., daily administration for at least three consecutive days, to treat erectile dysfunction using a chronic low dosing

regimen of about 1 to about 10 mg, and a maximum of about 10 mg/day, but rather teaches an "on demand" regimen at a relatively high dosage of at least 25 mg, and up to 100 mg, e.g., VIAGRA®.

WO'433 discloses the PDE5 inhibitor vardenafil and compounds of related structure. The compounds in WO'433 are disclosed as being useful in the treatment of cardiovascular diseases and urogenital diseases, like ED. However, WO'433 fails to cure the deficiencies of WO'003.

WO'433 teaches PDE5 inhibitors having an IC_{50} of 10 nM or less and administration of 0.001 to 50 mg/kg. See pages 48 and 49 of the attached, partial English-language translation of WO'433. However, the WO'433 disclosure, like WO'003, and known sildenafil references, does not teach or suggest a chronic dosing regimen of about 1 to about 10 mg, up to a maximum of about 10 mg per day, of a claimed PDE5 inhibitor for at least three consecutive days to improve vascular conditioning and treat erectile dysfunction.

WO'433, therefore, has the same deficiencies in WO'003, and a combination of WO'003 and WO'433 does not render the present claims obvious. *Neither* reference teaches or suggests the chronic treatment for ED using a presently claimed article of manufacture.

The examiner's statement that inclusion of a package insert including "indications and use" of a pharmaceutical compound is obvious because of the Remington publication is irrelevant. The examiner has failed to consider the indicia on the presently claimed insert, and its functional relationship to the oral dosage form, i.e., that the claimed oral dosage form

can be used in a chronic administration regimen to treat ED and improve vascular conditioning. Without the insert and the *claimed* indicia thereon, the user of the article would not be informed of the new and nonobvious function of the low oral dose form of PDE5 inhibitor present in the article of manufacture. As discussed above, applicants are not attempting to patent the printed matter on the insert, but *all* recited components (a)-(c) in the independent claims, and the additional recited features in the dependent claims.

The present invention relies on the discovery that improved vascular conditioning results from a chronic administration of a PDE5 inhibitor as defined in claims 1(a) and 2(a), for example, and in claims 10 and 13 in particular. This improved vascular conditioning is useful in treating sexual dysfunction when administered in a chronic regimen, as set forth on the claimed package insert. The present claims are both novel and nonobvious over other articles of manufacture for treating erectile dysfunction. In particular, novelty of the present claims does not lie in the mere presence of a container and an insert, but upon the identity of the PDE5 inhibitor, as defined in paragraph (a) of claims 1 and 2, in the container, *and* upon the *functional information* in the package insert, i.e., a chronic dosing regimen for treating erectile dysfunction. There is no known article of manufacture, or reference, that teaches or suggests these claimed features.

In summary, WO'003 and WO'433 disclose PDE5 inhibitors for treating erectile dysfunction and

provide a broad oral dosage range for an on-demand treatment regimen. Neither reference teaches or suggests a chronic dosing regimen of at least three consecutive days by the administration of up to 10 mg/day of a claimed PDE5 inhibitor, as presently recited in independent claims 1 and 2. WO'003 teaches *dividing* a daily dose into multiple doses, but fails to teach or suggest consecutive daily doses in a low dosage amount. In contrast, present-day PDE5-based treatments for erectile dysfunction rely upon "on demand" administration of a PDE5 inhibitor at a high dosage rate.

The cited references, alone or in combination, fail to teach or suggest a chronic dosing regimen, and no presently available treatments utilize a chronic dosing regimen. The references, alone or in combination, absolutely fail to provide any motivation for a person skilled in the art to consider a chronic dosing regimen, and provide no incentive for a person skilled in the art to reduce the PDE5 inhibitor dosage rate by at least 60% (e.g., 25 mg down to 1-10 mg) with any reasonable expectation of providing an article of manufacture useful in the treatment of erectile dysfunction.

In addition, the presently claimed invention meets an unsatisfied need in the art, i.e., a treatment of ED that permits more normal sexual relations with respect to spontaneity and not having to preplan sexual activity. The low dose of PDE5 inhibitor also reduces or eliminates various adverse side effects associated with a higher dose of other PDE5 inhibitors used to treat ED on demand. Accordingly, it is submitted that the rejection of all pending claims as being obvious

over WO'003 in view of WO'433 is in error and should be withdrawn.

Claims 10-13 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO'675) in view of VIAGRA Prescribing Information (VIAGRA), WO'433, and Remington's. In view of the amendments to the claims, for all the reasons set forth above, and for the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

Like WO'003, WO'675 teaches PDE5 inhibitors and further teaches that the inhibitors are useful in the treatment of ED. Claims 10, 11, and 13, as amended, recite compounds disclosed in WO'675. However, WO'675 fails to teach or suggest the claimed invention for the same reason as WO'003. In particular, there is *no* teaching or suggestion of a claimed chronic dosing regimen, and *no* motivation or incentive for a person skilled in the art to utilize the claimed chronic dosing regimen to treat ED with any reasonable expectation of success.

WO'433 has been discussed above, and its teachings do not overcome the deficiencies of WO'675 for the same reasons WO'433 does not overcome the deficiencies of WO'675. Also note that the present claims do not recite sildenafil or vardenafil.

Taking WO'675 and WO'433 together with VIAGRA still does not render the present claims obvious under 35 U.S.C. §103. VIAGRA teaches using a *minimum* 25 mg dose of sildenafil to treat ED in an *on-demand* regimen. VIAGRA is silent with respect to using a *maximum* dose of about 10 mg administered *chronically* as presently claimed. VIAGRA adds nothing to WO'675 and WO'433,

except for using a container for the oral dosage form. The VIAGRA insert does not provide for a chronic dosing regimen, but rather is limited to an on-demand regimen. VIAGRA, with WO'675 and WO'433, provides no motivation for a person skilled in the art to consider a presently claimed chronic dosing regimen using a low dose of PDE inhibitor.

The addition of Remington's to the combination of WO'675, WO'433, and VIAGRA still does not render the present claim obvious. Remington's merely teaches that an insert, or label, is required on a pharmaceutical product. The insert will contain directions for use and instructions, but *no* prior insert includes instructions for a chronic regimen to treat ED using a low dose of PDE5 inhibitor, as presently claimed.

The fact the 21 C.F.R. 201.57 requires a label is irrelevant. It is not the mere fact of having an insert as a component of the article that is important. What is important is the indicia on the insert and how it functionally relates to the oral dosage form and how it instructs individuals to treat ED in a new and unexpected manner, i.e., the claimed chronic dosing regimen using the specifically claimed PDE5 inhibitors. The insert and indicia thereon must be considered with *all* other claimed features, as set out in the above-discussed case law.

The examiner refers to different responses to different treatment regimens at pages 36 and 37 of the specification, and concludes that an increased response would be expected from more frequent administration of actives, e.g., the PDE inhibitor. The examiner further

contends that sildenafil is present in an article of manufacture in the doses presently claimed. The examiner's reasoning is erroneous.

First, the data on pages 36 and 37 show that a PDE5 inhibitor recited in the claims, and specifically in claim 13, effectively treats ED using 5 mg and 10 mg doses of the PDE5 inhibitor. These dosages are 80% and 60% *lower*, respectively, than the minimum 25 mg/dose required for sildenafil. This result alone is new and unexpected.

In addition, sildenafil is *not* known to be useful in the presently claimed doses, even when used in an "on-demand" regimen. The *lowest* on-demand dosage for sildenafil is 25 mg. The present claims recite a 1-to-10 mg dosage form administered and at a maximum dose of 10 mg/day. Again, this alone is a new and unexpected result.

Finally, the statement that an increased response would be expected with more frequent administration of the active is incorrect. First, the active must be administered in an amount sufficient to perform its intended function. Because sildenafil is administered in a minimum dose of 25 mg, it can be inferred that *lower* dosages are not effective. It is standard in the pharmaceutical industry to administer the lowest possible dose to achieve desired results and thereby avoid excessive administration of the active and avoid or minimize adverse side effects.

Second, the duration of beneficial results must be considered. Different compounds have a different effective life after administration. Sildenafil is taken on demand and has a "useful" period of action of

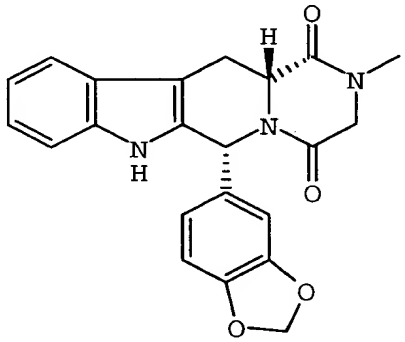
about four to six hours. An increased response is *not* expected from a more frequent administration of sildenafil. A more frequent administration for sildenafil would have to be every four to six hours to simply maintain sildenafil efficiency, and that dose would have to be at least 25 mg.

The presently claimed PDE5 inhibitors, at a low chronic dose, exhibit an ability to improve vascular conditioning, and they remain in the plasma to a sufficient extent, and for extended periods, to allow an effective chronic dosing regimen for the treatment of ED.

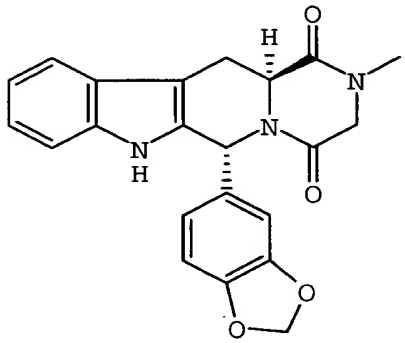
Accordingly, it is submitted that all pending claims are patentable under 35 U.S.C. §103 over the combination of WO'675, WO'433, VIAGRA, and Remington's, and that the rejection should be withdrawn.

Finally, applicants wish to address the examiner's response to previous arguments. With respect to claim 13, the compound recited therein is substantially different from compound of structural formula (I) in WO'003. The substitution of a six-membered ring for a five-membered ring is substantial. Even though some compounds of WO'003 have an IC_{50} of less than 10 nM, it is not taught or suggested that these compounds would have the required bioavailability for use in a 1 to 10 mg dosage form in the claimed chronic dosing regimen. WO'003 also does not teach or suggest that these compounds also do not possess the selectivity against PDE5 enzymes as recited in claim 5. Thus, additional factors in addition to IC_{50} values must be considered in selection of a PDE5 inhibitor useful in the present invention, as recited in the present claims.

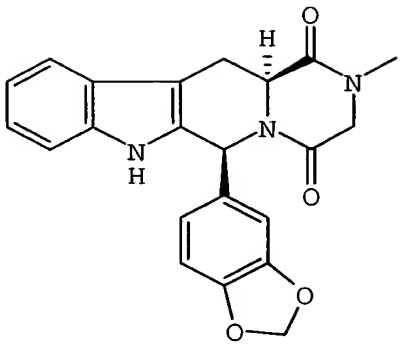
To further illustrate that subtle structural differences have a profound effect on PDE5 inhibition, the compound recited in claim 13 has an IC_{50} value of about 1 nM. The following stereoisomers of this compound i.e., the (R,S), (S,S), and (S,R) isomers, have IC_{50} values of 14, 6000, and 900 nM, respectively. The stereoisomers of a single compound, therefore, have profoundly different properties, and it cannot be stated that substitution of a six-membered ring for a five-membered ring of the WO'003 compounds would provide compounds having similar therapeutic effects.



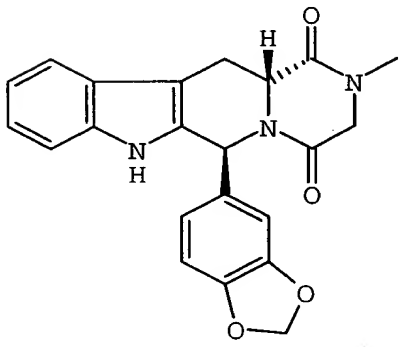
(R,R) isomer
(claim 13)



(R,S) isomer



(S,S) isomer



(S,R) isomer

In addition, the examiner's comments with respect to a package insert not further limiting an article of manufacture claim has been addressed above. In particular, the case law states that indicia must be considered with all other claimed elements of a combination.

It is submitted that all pending claims are now in proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is

urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE
Whitaker et al. U.S.S.N. 09/834,442

Claims 3, 4, and 12 have been cancelled without prejudice.

Claims 5-10, and 13 have been amended as follows:

5. (Twice amended) The article of manufacture of claim 1[,] or 2[, 3, or 4,] wherein the PDE5 inhibitor further has

(i) at least a 100 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE6, and

(ii) at least 1000 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE1c.

6. (Twice amended) The article of claim 1[,] or 2[, 3, or 4] wherein the oral dosage form comprises about 1 mg, about 2 mg, about 5 mg, or about 10 mg, of the PDE5 inhibitor.

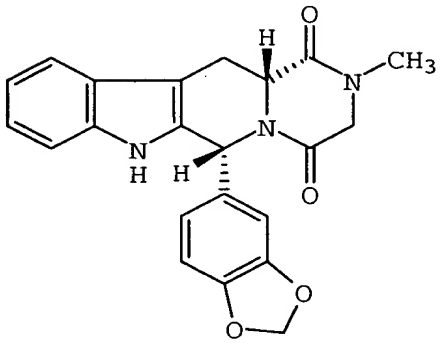
7. (Twice amended) The article of claim 1[,] or 2[, 3, or 4] wherein the chronic dosing regimen is a daily dosing regimen.

8. (Twice amended) The article of claim 1[,] or 2[, 3, or 4] wherein the chronic dosing regimen comprises administration of about 1 mg/day to about 10 mg/day of the PDE5 inhibitor.

9. (Twice amended) The article of claim 1[,] or 2[, 3, or 4] wherein the package insert provides a maximum dosage of the PDE5 inhibitor of about 10 mg per day.

10. (Amended) The article of claim 1[,] or 2[, 3, or 4] wherein the PDE5 inhibitor is selected from the group consisting of
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione[;]
~~5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl)phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;~~
~~5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and~~
~~5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one~~.

13. (Twice amended) The article of claim 1[,] or 2[, 3, or 4,] wherein the PDE5 inhibitor has the structure



New claims 19 and 20 have been added:

--19. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} for the inhibition of PDE5 less than 10 nM, and sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a chronic dosing regimen; and

(c) a container.

20. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} less than 10 nM, and a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a daily dosing regimen, and

(c) a container.--